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WHAT CAN WE LEARN FROM THE FACIT TRIAL: A RANDOMIZED, DOUBLE BLIND, CONTROLLED TRIAL

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Introduction

Observational studies show that low folate and elevated homocysteine concentrations are associated with poor cognitive performance in the general population. In a double blind randomized placebo-controlled trial we assessed whether 3-year folic acid supplementation (0.8 mg) improves cognitive performance in 818 men and women ages 50-70 years.

Methods

Assuming that high concentrations of plasma total homocysteine were a risk factor, we selected participants expected to benefit from folic acid's homocysteine-lowering effect. Participants with concentrations of plasma total homocysteine <13 μmol/L (73rd percentile of those screened) were excluded. We excluded participants with possible elevated homocysteine concentrations due to factors, other than sub-optimal folate concentrations including: serum vitamin B_{12} <200 pmol/L (10th percentile of those screened; vitamin B_{12} concentrations <160 pmol/L indicated vitamin B_{12} deficiency); self-reported medical diagnosis of renal or thyroid disease; or self-reported use of medications that influence folate metabolism (1). In addition, we excluded participants with self-reported intestinal disease and participants who reportedly used B vitamin supplements. At the time of our study folic acid fortification of foods was prohibited in the Netherlands.

All participants underwent the cognitive performance assessments after an overnight fast, followed by a glass of juice and a bread product for breakfast. The tests have been previously described (2) Trained research assistants administered the tests during a 40-minute session; they used a standard text to instruct participants. A third research assistant periodically observed the testing to ensure that the 2 research assistants did not deviate from the protocol. All cognitive tests were conducted in the same room with the same props.

The outcome of the study was the difference between the folic acid and placebo group in the 3-year change in performance on the domains: memory, sensorimotor speed, complex speed, information processing speed and word fluency. Seventeen participants lost to follow-up were given the median test score of the total population at the end of the study. Analyses were conducted on an intention-to-treat basis. Statistical significance was defined as $p<0.05$ (two-tailed) and no adjustments were made for multiple testing.

Results

Serum folate concentrations increased 5-fold and plasma total homocysteine concentrations decreased by 26% in participants on folic acid versus placebo.

Folic acid significantly improved memory (difference in Z-scores 0.132, 95%CI 0.032; 0.233), information processing speed (difference in Z-scores 0.087, 95%CI 0.016; 0.158) and sensorimotor speed (difference in Z-scores 0.064, 95%CI -0.001; 0.129) (Table 1). Folic acid did not affect complex speed or word fluency. Folic acid improved performance on several cognitive functions that tend to decline with age.

In addition to memory and information processing speed, sensorimotor speed significantly improved ($p<0.05$) when other imputation techniques were used (e.g. last value carried forward, expectation maximization); when 17 participants lost to follow up were excluded from the analyses; or when 7 participants with initial Mini-Mental State Examination scores <24 points were excluded from the analyses. Finally, at baseline, a greater percentage of participants with a low educational level, an important determinant of cognitive performance, were randomized into the folic acid group. In addition, a higher percentage of participants in the folic acid group had dyslipidemia and self-reported vascular disease. Our results did not change when we adjusted for these variables.

To illustrate the relevance of our findings we compared the unstandardized beta of age—adjusted for sex, education and treatment, calculated using linear regression models with initial performance as the dependent variable—with the treatment effect. Three-year folic acid supplementation gives an individual the performance of someone 4.7 years younger for memory (95%CI 1.1; 8.3), 1.7 years younger for sensorimotor speed (95%CI -0.04; 3.4), 2.1 years younger for information processing speed (95%CI 0.4; 3.7) and 1.5 years younger for global cognitive function (95%CI 0.1; 2.8).

In contrast to the effects of folic acid on the cognitive tests, we did not detect an effect on Mini-Mental State Examination performance ($p=0.63$). The median score after 3 years was 29 points (28 to 30) and the range was 21 to 30 points in the folic acid group vs. 16 to 30 points in the placebo group.

Table 1
Mean (standard deviation) change in cognitive performance within groups over 3 years and mean difference (95% confidence interval) in cognitive change attributed to folic acid supplementation

Folic acid n=405				**Placebo n=413**				**Folic acid vs. Placebo**	
Year 0	**Year 3**	**3-year change in cognitive performance**	**P value***	**Year 0**	**Year 3**	**3-year change in cognitive performance**	**P value***	**Mean difference (95% confidence interval)**	**P value****
Global cognitive function, Z-score									
0.006	0.073	0.067	<0.001	-0.048	-0.031	0.017	0.287	0.050	0.033
(0.673)	(0.694)	(0.338)		(0.672)	(0.701)	(0.332)		(0.004; 0.096)	
Memory, Z-score									
-0.207	0.273	0.480	<0.001	-0.206	0.142	0.348	<0.001	0.132	0.010
(0.959)	(0.965)	(0.724)		(0.883)	(0.961)	(0.737)		(0.032, 0.233)	
Sensorimotor speed, Z-score									
0.054	0.011	-0.042	0.063	0.019	-0.087	-0.106	<0.001	0.064	0.055
(0.706)	(0.753)	(0.458)		(0.836)	(0.819)	(0.490)		(-0.001, 0.129)	
Complex speed, Z-score									
0.053	0.026	-0.027	0.405	-0.008	-0.072	-0.064	0.029	0.037	0.40
(0.803)	(0.868)	(0.651)		(0.879)	(0.865)	(0.593)		(-0.049, 0.122)	
Information processing speed, Z-score									
0.093	0.021	-0.072	0.005	0.024	-0.135	-0.159	<0.001	0.087	0.016
(1.008)	(0.967)	(0.513)		(1.008)	(1.008)	(0.517)		(0.016, 0.158)	
Word fluency, Z-score									
0.038	0.036	-0.002	0.961	-0.070	-0.002	0.068	0.108	-0.070	0.245
(1.056)	(1.029)	(0.864)		(0.959)	(0.953)	(0.859)		(-0.188, 0.048)	

* One sample t-test(0); ** Independent sample t-test.

Discussion

The present study may have yielded demonstrable effects of folic acid on cognitive function because we used sensitive tests which exist in parallel versions. We also improved the robustness of the underlying cognitive constructs by clustering raw test scores over several tests in compound performance measures. This decreased variation associated with the individual tests. Finally, clustering of raw tests scores limited our cognitive performance outcomes to 5 a priori defined outcomes.

In contrast to other trials we were able to detect an effect of folic acid on several cognitive functions probably due to a number of reasons. First, assuming that elevated plasma total homocysteine concentrations are a causal risk factor for cognitive decline, we selected a population likely to benefit from folic acid supplementation. Second, we had a relatively large study population and supplemented for a relatively long period. Third, although we did not attempt to measure the prevalence of dementia at baseline nor its incidence during the duration of the trial, it is unlikely that our population has many participants cognitively impaired or demented, as the general performance on a dementia screening test like the Mini-Mental State Examination were high, both at the beginning and at the end of the study. It is plausible that treatment with folic acid or other B vitamins may be too late in populations with mild cognitive impairment and dementia. Finally, sensitive tests as our own, not the commonly used Mini-Mental State Examination, a dementia screening tool, were needed to detect the subtle effects of B vitamins on cognitive aging. Importantly, given the general lack of positive findings from other trials (see Table 2) and the multiple comparisons made in our trial, our results need to be confirmed by other investigators to ascertain whether our statistically significant positive effects of folic acid on cognitive performance were due to type 1 error.

A strength of our study is the low attrition rate, which otherwise may bias studies of cognitive change. Participants with poor cognitive function are likely to withdraw from studies (13). In our study, the 12 participants in the folic acid group and 5 participants in the placebo group who did not return for the end measurements scored lower (0.558 Z-score, 95%CI 0.116; 1.000) on baseline tests of memory only. This is unlikely to have affected our estimates for several reasons: the effect of folic acid supplementation on memory did not depend on baseline performance on the memory tests (data not shown), the number of participants lost to follow-up was minimal and the effect estimates based on participants with follow-up data were similar to the intention-to-treat analyses. A second strength was the standardized test conditions that reduced variation due to factors like caffeine and varying breakfasts (14).

Table 2
Summary of randomized controlled trials that have examined folic acid-containing supplements on cognitive function

Author	Time	N at follow-up (in analyses)	Age (y)	Population type	Dose of folic acid (vs. placebo)	Type of cognitive tests	Conclusion
Folic acid only							
Fioravanti et al. (3)	60 d	29	80±6	Patients with memory complaints, Mini-Mental State Examination score between 16-24, mild to moderate cognitive decline based on Global Deterioration Score, 70-90 y, serum folate <7 nmol/L	15 mg/d FA	1. Randt Memory Test a. acquistion & recall b. delayed recall c. memory index d. encoding factor e. cognitive efficiency f. attention efficiency	- Folic acid improved attention efficiency score ($p<0.05$). - When taking into account baseline folate status, folic acid improved acquisition and recall ($p<0.007$), delayed recall ($p<0.007$) memory index ($p<0.002$), encoding ($p<0.005$)
Sommer et al. (4)	10 w	7	77±4	Patients meeting the DSM-III-R criteria for dementia, ≥65 y, sub-optimal folate (serum folate 2-5 ng/ml, red blood cell folate 127-452 ng/ml), B_{12} >200 pg/ml	2x 10mg/d FA	1. Wechsler Memory Scale 1a. logical memory subtest 1b. associate learning subtest 2. Boston Naming test 3. Controlled Oral Word Association test 4. Trail making test 5. Finger Tapping test 6. Wechsler Adult Intelligence Scale-revised (composite of information, vocabulary and similarities sub-tests) 7. Benton Visual Retention test	Folic acid seemed to decreased performance on associate learning subtest of Weschler Memory Scale ($p=0.08$) and Trails B ($p=0.08$).
Folic acid with other B vitamins							
Eussen et al. (5)	24 w	162	82±5	Mini-Mental State Examination ≥ 19, ≥70 y, sub-optimal vitamin B12 status (B12 100-200 pmol/L OR B12 200-300 pmol/L, methylmalonic acid ≥0.32 mmol/L, creatinine ≤120 mmol/L)	0.4 mg/d	Domains based on clustering of similar tests 1. attention 2. construction 3. sensomotor speed 4. memory 5. executive function	Compared to placebo or to vitamin B_{12} only, no effect of folic acid on cognitive domains.
McMahon et al. (6)	2 y	253	74±6	≥65 y, homocysteine ≥13 mmol/L	1 mg/d	1. Mini-Mental State Examination 2. Wechsler Paragraph Recall 3. Category Word Fluency 4. Rey Auditory Verbal Learning 4a. composite of trials 1-5 4b. trial 7 5. Raven's Progressive Matrices 6. Controlled Oral Word Association 7. Reitan Trail Making, part B 8. Composite score of all tests	- General trend towards decreased performance on tests. In crude analyses statistical significance was reached for the Reitan trail Making test (part B) (7% slower, 95%CI 2; 13%) and Wechsler Paragraph Recall test (mean difference -1.19, 95%CI -2.30; -0.04 standard deviations). - After adjustment for baseline performance, sex and education the composite score of all tests was lower in the group supplemented with folic acid compared to placebo (-0.11, 95%CI -0.22; 0 standard deviations).
Stott et al. (7)	1 y	167	75±6	Mini-Mental State Examination ≥ 19, ischemic vascular disease, ≥65 y, red blood cell folate ≥280 ng/mL, vitamin B_{12} ≥250 pg/mL	2.5 mg/d	1. Telephone Interview for Cognitive Status 2. Letter Digit Coding	No effect.

Table 2 (following)

Author	Time	N at follow-up (in analyses)	Age (y)	Population type	Dose of folic acid (vs. placebo)	Type of cognitive tests	Conclusion
Bryan et al. (8)	5 w	104	51±20	Healthy women	0.75 mg/d FA	1. Boxes test 2. Digit Symbol Coding, 120s 3. Symbol search 4. Digit Span Backward 5. Letter-Number Sequencing 6. Rey Auditory-Verbal Learning test 6a. Immediate recall 6b. Delayed recall 7. Digit Symbol Coding, symbol recall 8. Activity recall 9. Stroop test 10. Self-ordered pointing task 11. Uses for common objects 12. Trail Making test 13. Verbal Fluency test 14. Excluded Letter Fluency 15. WAIS-III Vocabulary 16. Spot-the-Word test	- Folic acid decreased Verbal Fluency performance ($p<0.05$). - When stratifying by age, folic acid improved Rey Auditory-Verbal Learning test (recognition task) in older participants (>65 y, $p<0.05$).
Toole et al. (9)	2 y	3097	66±10	Prior stroke, homocysteine > ~9 mmol/L	2.5 mg/d FA vs. 0.02 mg/d FA	1. Mini-Mental State Examination 1. Mini-Mental State Examination	No effect. No effect.
Vital Trial Collaborative Group (10)	12 w	128	Range 56-89	Mini-Mental State Examination score 12-26 or mild cognitive impairment assessed by modified Telephone Interview of Cognitive Status	2 mg/d FA	2. Alzheimer's Disease Assessment Scale (cognitive part)	
Lewerin et al. (11)	4 m	171-179	76±4	Community-dwelling	0.8 mg/d FA	1. Digit Span Forward 2. Digit Span Backward 3. Identical forms 4. Visual reproduction 5. Synonyms 6. Block design 7. Digit Symbol, 90s 8. Thurstone's Picture Memory test 9. Figure Classification	Folic acid improved performance on identical forms and synonyms ($p<0.05$).
Obeid et al. (12)	45 d	69	80±6	Mini-Mental State Examination score >15, >65 y	5 mg/d FA (oral) 1.1 mg FA (intravenously 3x week for 3 weeks)	1. Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multiinfarct Dementia and Dementia (SIDAM) 2. Orientation abilities 3. Memory 4. Intellectual abilities	- Didn't report treatment effect, only differences in performance within groups

Abbreviation: FA folic acid; DSM-III-R: Diagnostic and Statistical manual of Mental Disorders, 3rd edition revised; 95%CI: 95% confidence intervals

Our study had limitations. First, it was conducted in participants with elevated plasma total homocysteine concentrations: 3,044 participants out of 4,200 participants were excluded from the study because of low plasma total homocysteine concentrations. Thus, the effect of folic acid supplementation on cognitive function may be greater than would be expected in populations with lower plasma total homocysteine concentrations, e.g. in countries like the United States with mandated fortification of flour with folic acid. Second, our findings pertain only to vitamin B_{12}-replete individuals. It has been suggested that folic acid supplementation exacerbate neurological symptoms in subjects with vitamin B12 deficiency (15). The possibility of folic acid mediated exacerbation of neuropathological conditions in subjects with low levels of vitamin B12 needs to be addressed by studies that monitor both vitamin B12 status and neurological function. Our data show that folic acid supplementation improved sensorimotor speed (difference in Z-score 0.112 (95%CI 0.001; 0.223) and information processing speed (difference in Z-score 0.190 (95%CI 0.055; 0.325)) in 230 participants with initial low-normal concentrations of vitamin B_{12} (<250 pmol/L), but not in 588 participants with vitamin B_{12} concentrations ≥250 pmol/L (difference in Z-scores 0.046 (95%CI -0.033; 0.126) and 0.048 (95%CI -0.036; 0.131), respectively). As an improvement to our own study, transcobalamin in addition to vitamin B_{12}, should be measured, as the former is a better marker of vitamin B_{12} status.

Will folic acid supplementation lead to a decreased incidence of dementia? While some have argued that cognitive decline is a beginning of a continuum leading to dementia, (16) others have argued that the etiology of age-related cognitive decline differs from that of dementia (17) and that age-related cognitive decline is not an early state of mild cognitive impairment or dementia (18). Cognitive tests differ in their ability to identify individuals who worsen to more advanced states like mild cognitive impairment or dementia. Of our test battery, memory is most clinically relevant. Memory can distinguish between cognitively normal and cognitively impaired subjects (19). Memory storage (delayed recall), in particular, can distinguish between subjects with non-progressive mild cognitive impairment and pre-clinical Alzheimer's disease (20). We found that 3-year folic acid supplementation improves performance on the delayed recall sub-test of the 15 Word Learning test by 0.47 words (95% CI 0.14; 0.79 words, p=0.005). This improvement is similar to a performance of an individual 6.9 y younger (95%CI 2.1; 11.8). Whether folic acid supplementation will prevent dementia is uncertain.

Conclusion

We show that 3-year folic acid supplementation improves performance on tests measuring sensorimotor and information processing speed and memory in older adults with elevated total homocysteine concentrations, domains known to decline with age. Randomized, controlled trials are currently underway which examine the effect of homocysteine-lowering on recurrent vascular disease and cognitive function assessed by the Mini-Mental State Examination or modifications thereof; these and other homocysteine-lowering trials should include sensitive measures of cognitive function. In addition, trials similar to our own need to be repeated in other populations which give more insight into the clinical relevance of folic acid supplementation, like in populations with mild cognitive impairment and dementia.

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